UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/721,742	11/26/2003	Masako Nozaki	NOZAKI8.1A	3949

1444 7590 05/17/2006

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,742	NOZAKI, MASAKO	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-18 and 20-24* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,15-18,20 and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,9,11-14 and 21* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *See Continuation*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Attachment (3): Information Disclosure Statements filed November 26, 2003 (one page); April 2, 2004 (one page); and September 24, 2004 (one page).

DETAILED ACTION

Claims 1-9, 11-18 and 20-24 are presented for examination.

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/496,677, filed August 21, 2003, and U.S. Provisional Patent Application No. 60/429,558, filed November 29, 2002. Acknowledgement is further made of Applicant's claim for priority under 35 U.S.C. 119(a-d) to Japanese Patent Application No. 142759, filed May 20, 2003. Applicant's Information Disclosure Statements (IDS) filed November 26, 2003 (one page), April 2, 2004 (one page) and September 24, 2004 (one page) have each been received and entered into the application. As reflected by the attached, completed copies of form PTO/SB/08A (three pages total), the Examiner has considered the cited references.

Applicant's response and amended claim set filed April 13, 2006 to the requirement for restriction/election dated March 16, 2006 has also been received and entered into the application. Accordingly, Applicant has amended claims 1, 17 and 21 and cancelled claims 10 and 19.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group III (claims 5-6), drawn to a method for treating or inhibiting the development of inflammation due to trauma to the brain, which may result from surgery, in the reply filed April 13, 2006 has been acknowledged by the Examiner. Claims 1-2, 8-9, 11-14 and 21 are identified as linking claims and will be examined with the elected group.

Applicant's traversal of the election of species requirement as it applies to Group III has

been noted. It is agreed that the election of species requirement does not apply to the election of Group III. For this reason, Applicant is not required to elect a single species of sepsis etiology or inflammation-inducing agent as set forth in the restriction requirement of March 16, 2006.

Therefore, for the reasons above and those made of record at pages 2-7 of the previous Office Action dated March 16, 2006, the restriction requirement is deemed proper and is made **FINAL**.

Claims 3-4, 7, 15-18, 20 and 22-24 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected subject matter.

The claims corresponding to the elected subject matter are 1-2, 5-6, 8-9, 11-14 and 21 and such claims are herein acted on the merits.

Applicant's Claim for Priority under 35 U.S.C. 119

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(a-d) and 119(e) is acknowledged. Applicant is reminded that the later-filed application must be an application for patent for an invention that has been disclosed in the prior application (i.e., the provisional or foreign application(s)). The disclosure of the invention in the provisional or foreign application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Receipt of the certified copy of Japanese Patent Application No. 142759 (filed May 20, 2003), submitted under 35 U.S.C. 119(a)-(d), has been placed of record in the file.

Applicant has complied with the conditions for receiving the benefit of an earlier filing

date under 35 U.S.C. §119(e) as it is claimed to U.S. Provisional Patent Application No. 60/429,558, filed November 29, 2002, because the subject matter disclosed in this application contains sufficient written support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter of claims 1-2, 5-6, 8-9 and 14. However, Applicant is advised that neither disclosures of U.S. Provisional Patent Application Nos. 60/429,558, filed November 29, 2002 and 60/496,677, filed August 21, 2003 contain sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter of present claims 11-13 and 21.

Accordingly, the subject matter of present claims 1-2, 5-6, 8-9 and 14 is afforded the effective filing date of November 29, 2002 and the subject matter of present claims 11-13 and 21 is afforded the effective filing date of May 20, 2003.

Objections to the Specification

Applicant's claim for priority has been noted as it appears at paragraph [0001] of the specification, but fails to recite Applicant's claim for priority under 35 U.S.C. 119(a-d) to Japanese Patent Application No. 142759, filed May 20, 2003. Applicant may wish to consider amending the priority data at page 1 of the specification in the following manner. Applicant is reminded that the adoption of this suggestion does not necessarily equate to the claims being free of the cited prior art.

---[0001] This application claims the benefit of priority under 35 U.S.C. §119(e) from U.S. provisional application nos. 60/429,558, filed November 29, 2002, and 60/496,677, filed August 21, 2003, and claims the benefit of priority under 35 U.S.C. §119(a-d) to Japanese Patent

Application No. 142759, filed May 20, 2003, the entire contents of which are incorporated herein by reference.---

Applicant has amended paragraph [0061] at line 4 of page 26 to read on pranlukast administered at a lower dosage amount of 0.003 mg/kg, not 0.03 mg/kg as originally stated. Such a change is in accordance with the teachings of Zhang et al. However, Applicant has failed to amend paragraph [0061] at line 9 of the specification to be consistent with this amount as taught by Zhang et al. Appropriate correction is required.

The amendment to the drawings filed April 2, 2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows:

(1) The amendment to Figure 2 changes the units of pranlukast from (mol/kg) to "(mmol/kg)".

Applicant does not provide a reference to any supporting disclosure either in the present specification or in the priority documents that would indicate that this was a typographical error and that this change does not add material to the specification that was not present or suggested in the specification as originally filed.

Applicant is invited to provide evidence supporting this change or is alternatively required to cancel the new matter in the reply to this Office Action.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5, 8-9, 11-14 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi et al. ("Effect of Leukotriene Antagonist on Experimental Delayed Cerebral Vasospasm", *Neurosurgery*, 31(3), 1992; cited by Applicant) in view of Zhang et al. ("Neuroprotective Effect of ONO-1078, a Leukotriene Receptor Antagonist, on Focal Cerebral Ischemia in Rats", *Acta Pharmacologica Sinica*, Oct 2002; cited by Applicant) and The Merck Manual of Diagnosis and Therapy (1999).

Kobayashi et al. teaches the administration of ONO-1078 (paragraph bridging cols.1-2 at page 551), a compound that blocks both LTC4 and LTD4 induced increased in vascular permeability (last paragraph, col.1 at page 551), in an amount of 0.3 mg/kg once a day for 7 days (paragraph 1, col.2 at page 551), to dogs with cerebral vasospasm subsequent to subarachnoid hemorrhage (abstract at page 550), which was shown to have inhibiting effects on the development of vasospasm following subarachnoid hemorrhage (paragraph bridging cols. 1-2 at page 554; see present claims 1 and 21). Kobayashi et al. further teaches that the capillaries have increased levels of LTC4 after subarachnoid hemorrhage and loss of gamma-glutamyl transpeptidase after a cerebral insult and suggests a significant role of LTC4 on the development of increased capillary permeability during cerebral injury that ultimately leads to cerebral edema (paragraph 2, col.1 at page 554).

Zhang et al. is cited to show that ONO-1078 is synonymous with pranlukast (see abstract at page 871).

The differences between the Kobayashi et al. reference and the presently claimed subject matter lie in that the reference fails to teach:

(i) the subarachnoid hemorrhage is due to brain trauma (see present claims 2 and 5);

(ii) repeated administration of pranlukast until the white blood cell count reaches a normal level is the cerebrospinal fluid (see present claim 8); administration preoperatively before brain surgery or before an invasive brain operation (see present claim 9); or the present claimed dosage ranges of 100-2000 mg/day (see present claim 11); 200-1000 mg/day (see present claim 12); or 400-800 mg/day (see present claim 13); or

(iii) the administration of pranlukast to a human (see present claim 14).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) The Merck Manual of Diagnosis and Therapy (1999; p.1457-1459) provides teachings that head trauma is the most common cause of subarachnoid bleeding. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the efficacy shown by pranlukast in inhibiting the development of cerebral vasospasm subsequent to subarachnoid hemorrhage would have been reasonably expected to demonstrate the same, or substantially similar, efficacy in treating the complications of inflammation and vasospasm

associated with subarachnoid hemorrhage as it results from blunt trauma to the head, since this was known in the art to be the most common cause of subarachnoid bleeding.

(ii) The determination of the optimum regimen for administration of the active agent ONO-1078 (i.e., pranlukast) would have been *prima facie* obvious to, and a matter well within the purview of, one of ordinary skill in the art at the time of the invention. As taught by Kobayashi et al. at page 554, the presence of leukotrienes chemically mediates inflammatory response and enhances leukocyte adhesion in the subarachnoid space (see page 554, column 1, last paragraph). In light of such a teaching, it would have been *prima facie* obvious to one of ordinary skill in the art to administer ONO-1078 regularly until the presence of WBCs in the CSF was reduced, because the level of WBCs would have been a direct indicator of the level of leukotrienes in the CSF and whether the inflammatory response due to the subarachnoid hemorrhage was improving or worsening.

Moreover, the administration of ONO-1078 prior to brain surgery would also have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention because Kobayashi et al. clearly shows the efficacy of ONO-1078 in inhibiting the development of delayed cerebral vasospasm subsequent to subarachnoid hemorrhage and suggests the efficacy of ONO-1078 in antagonizing the inflammatory reaction subsequent to subarachnoid hemorrhage. The Merck Manual of Diagnosis and Therapy provides teachings that surgical procedures following development of a subarachnoid hemorrhage to obliterate, trap or clip the aneurysm minimizes the risk of rebleeding and may reduce the risk of postoperative vasospasm and infarction (see page 1426). The skilled artisan would have readily appreciated that the effects of ONO-1078 in lessening or inhibiting the development of complications associated with

subarachnoid hemorrhage, such as cerebral vasospasm, as shown by Kobayashi et al. would have been reasonably expected to concomitantly reduce the cerebral complications, i.e., cerebral vasospasm or re-bleeding, that typically result from subarachnoid hemorrhage when administered pre-operatively prior to brain surgery because it was recognized in the art that both ONO-1078 and neurosurgical procedures following subarachnoid hemorrhage were known to reduce the risk of, for example, cerebral vasospasm. In light of such, one of ordinary skill in the art would have reasonably expected, at minimum, that the administration of ONO-1078 prior to or with surgical correction would have achieved, at minimum, a greater effect when combined than when either therapy was used alone.

In addition, the determination of the optimum dosage range to treat cerebral complications associated with subarachnoid hemorrhage with the presently claimed active agent would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed specific dosage range is not seen to be inconsistent with that which would have been determined by the skilled artisan.

Applicant's attention is drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to

determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Although the present claims are drawn to mg/day dosage amounts, such a motivation is nonetheless relevant.

Applicant is further reminded that should he rely upon the fact that a particular amount of pranlukast is critical to the invention, Applicant must make an objective showing that the claimed range achieves unexpected results relative to the prior art range [*In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)] and that the unexpected results demonstrate a marked improvement over that achieved using the amounts of the prior art such that the difference shown in actually a difference in kind and not just a difference in degree [*In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974)]. Furthermore, Applicant is further advised that should he rely upon unexpected results to patentably distinguish over the prior art, the present claims must be limited to that embodiment which is, in fact, unexpected.

(iii) It is well recognized in the art that in vivo studies in animals, such as dogs or mice, commonly precede testing of pharmaceutical agents in humans. In vivo studies serve as a reasonable predictor of efficacy in a human model by providing a basis for determining the efficacy of such an agent in a similar physiological environment in vivo and extrapolating such efficacy to an genetically similar animal model. Although Kobayashi et al. teaches the efficacy of the compound pranlukast in vivo for treating cerebral vasospasm subsequent to subarachnoid hemorrhage in dogs, such results raise the reasonable expectation of success that such a compound would have been reasonably expected to have the same or substantially similar

activity in vivo in humans, absent factual evidence to the contrary. In fact, Kobayashi et al. expressly suggests that intravenous administration of ONO-1078 daily after the initial blood injection may inhibit the development of delayed cerebral vasospasm. Such a teaching is undoubtedly a suggestion to adapt the agent for therapeutic use in vivo in humans with the reasonable expectation of substantial efficacy in treating the cerebral complications associated with subarachnoid hemorrhage.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. ("Neuroprotective Effect of ONO-1078, a Leukotriene Receptor Antagonist, on Focal Cerebral Ischemia in Rats", *Acta Pharmacologica Sinica*, Oct 2002; cited by Applicant).

Zhang et al. teaches a method of administering ONO-1078 (i.e., pranlukast) to rats with focal cerebral ischemia (see abstract at page 871), wherein the treatment with ONO-1078 at 0.01-10 mg/kg significantly inhibited the enlargement of the ischemic hemisphere, which represented brain edema (see paragraph bridging page 873-874).

The differences between the Zhang et al. reference and the presently claimed subject matter lie in that the reference fails to teach the presently claimed dosage range of 400 mg/day to 800 mg/day.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because the determination of the optimum dosage range to treat brain inflammation with the presently claimed active agent would have been a matter well within the purview of one of

ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed specific dosage range is not seen to be inconsistent with that which would have been determined by the skilled artisan.

Applicant's attention is drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages...Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Although the present claims are drawn to mg/day dosage amounts, such a motivation is nonetheless relevant.

Applicant is further reminded that should he rely upon the fact that a particular amount of pranlukast is critical to the invention, Applicant must make an objective showing that the claimed range achieves unexpected results relative to the prior art range [*In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)] and that the unexpected results demonstrate a marked improvement over that achieved using the amounts of the prior art such that the difference shown in actually a difference in kind and not just a difference in degree [*In re*

Waymouth, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974)]. Furthermore, Applicant is further advised that should he rely upon unexpected results to patentably distinguish over the prior art, the present claims must be limited to that embodiment which is, in fact, unexpected.

Subject Matter of Present Claim 6 Not Taught or Suggested by the Prior Art

It is noted that a comprehensive and reasonable search conducted by the Examiner has determined that the prior art was not aware of a motivation to use the presently claimed active agent pranlukast to treat brain trauma as it results from brain surgery. Moreover, it is noted that any motivation or suggestion to combine the cited references to arrive at the conclusion that the use of pranlukast for the treatment of brain trauma resulting from brain surgery cannot be located in the prior art.

In particular, it is noted that the cited references are drawn to the treatment of cerebral vasospasm as it results from subarachnoid hemorrhage. While subarachnoid hemorrhage is commonly treated in the art via surgical methods of obliterating, trapping or clipping the aneurysm from which it results, it is noted that the subarachnoid hemorrhage does not expressly result from brain surgery itself. In fact, The Merck Manual of Diagnosis and Therapy expressly states that subarachnoid hemorrhage results from spontaneous hemorrhage resulting from congenital intracranial aneurysm, mycotic or arteriosclerotic aneurysm, arteriovenous malformation, or hemorrhagic disease (see Merck, p. 1425). In light of such a teaching, it would be in error to conclude that the treatment of brain trauma as it results from surgery because such a conclusion would not logically follow from the prior art teachings of the cited references that expressly teach subarachnoid hemorrhage resulting from distinctly different etiologies. In the

absence of any additional prior art that would either render this limitation anticipated or obvious under 35 U.S.C. 102 or 103, it is noted that the subject matter of present claim 6 does not appear to be taught or suggested by the prior art. For this reason, claim 6 is rejected to as depending from a rejected base claim, but would be otherwise allowable if written in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Rejection of claims 1-2, 5, 8-9, 11-14 and 21 is deemed proper.

Claims 3-4, 7, 15-18, 20 and 22-24 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b).

Claim 6 is objected to for depending from a rejected base claim.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

May 11, 2006

Ardin H. Marschel 5/15/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER